Exhibit 9 – Part 4 of 7

D. 2-(t-Butyloxycarbonylamino)-4-(Cbz-((β,β-di-Me)-β-Ala)-leucinyl-amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 78C was coupled to the resultant compound of Example 11 to give the desired compound.

Example

A. (3,4-cis-Dihydroxypyrrolidinylcarbonyl)-leucine Methyl Ester.

A suspension of L-leucine methyl ester hydrochloride (10 g) in toluene (f200 ml) was heated to 100° C while phosgene gas was bubbled into the reaction mixture. After approximately 2 h the mixture became homogeneous. The bubbling of phosgene was continued for 15 more minutes keeping the temperature at 100° C. The toluene was then evaporated and the residue chased with benzene several times. The isocyanate from L-Leu-OCH_3 was then dissolved in 100 ml of methylene chloride and 1.1 equivalent of 3-pyrroline (75% pure) was added dropwise at 0° C. After 15 min, the reaction mixture was washed with 0.5 N HCl and methylene chloride. The organic layer was washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent gave 3-pyrrolinylcarbonyl-Leu-methyl ester which was cis-hydroxylated under the following conditions: 2.5 g of the 3-pyrrolinylcarbonyl-Leu-methyl ester was dissolved in 50 ml of THF and 1 ml of a 2.5% solution of OsO_4 in t-butanol was added, followed by 1.15 g of N-methylmorpholine-N-oxide. After 1 h, the solvent was evaporated and the residue dissolved in 150 ml of ethyl acetate, washed with dilute Na_2SO_3 solution and satd. $NaHCO_3$ solution, and then dried over $MgSO_4$. Evaporation of the solvent gave a crude compound which was purified by SiO_2 column chromatography to give the desired compound.

B. (3,4-cis-Dihydroxypyrrolidinylcarbonyl)-leucine.

The resultant compound of Example 79A was hydrolyzed according to the procedure of Example 78C to provide the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-((3,4-cis-dihydroxypyrrolidinylcarbonyl)-leucinyl-amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 79B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 80

2-(N-(6-Aminohexanoyl)-valinyl-valinyl-amino)-4-(N-(5-carboxypentanoyl)-valinyl-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 71C with the resultant compound of Example 74 gave the desired compound.

Example 81

1,3-Di-(S-phenylthiol-2-((methoxy)methoxy)propane.

Using the procedure of Example 51 but replacing 1,5-diphenyl-3-pentanol with the resultant compound of Example 15 gave, after silica gel chromatography using 15% ethyl acetate in hexane, 44 mg (31%) of the desired compound (R_f 0.27, 20% ethyl acetate in hexane). ^{1}H NMR ($CDCl_3$) δ 3.21 (dd, J = 15, 6 Hz, 2 H), 3.26 (dd, J = 15, 6 Hz, 2 H), 3.40 (s, 3 H), 3.91 (pentet, J = 6 Hz, 1 H), 4.68 (s, 2 H), 7.15-7.35 (m, 10 H). Mass spectrum $(M + NH_4)^+$ = 338.

Example 82

1,3-Diphenoxy-2-((methoxy)methoxy)propane

Using the procedure of Example 51 but replacing 1,5-diphenyl-3-pentanol with the resultant compound of Example 4 gave, after silica gel chromatography using 10% ethyl acetate in hexane, 80 mg (49%) of the desired compound (R_f 0.42, 20% ethyl acetate in hexane). ^{1}H NMR ($CDCl_3$) δ 3.44 (s, 3 H), 4.18 (dd, J = 10, 6 Hz, 2 H), 4.22 (dd, J = 15, 6 Hz, 2 H), 4.33 (pentet, J = 6 Hz, 1 H), 4.85 (s, 2 H), 6.9-7.0 (m, 6 H), 7.25-7.35 (m, 4 H). Mass spectrum $(M + NH_4)^+$ = 306.

Example 83

A. ((4-Thiomorpholinyl)carbonyl)-leucine Methyl Ester.

A suspension of L-leucine methyl ester hydrochloride (6 g) in toluene (125 ml) was heated to 100° C and phosgene gas was bubbled into the reaction mixture. After approximately 1.5 h, the mixture became homogeneous. The bubbling of phosgene was continued for 10 more min. The solvent was then evaporated and the residue chased with benzene several times. The residue was then dissolved in 100 ml of methylene chloride, cooled to 0° C, and treated dropwise with 1.1 equivalent of thiomorpholine. After 10 min the solution was washed with 1N HCl and the organic layer was dried with $MgSO_4$. Evaporation of solvent gave the desired compound.

B. (4-Thiomorpholinylcarbonyl)-leucine.

The resultant compound of Example 83A ws hydrolyzed according to the procedure of Example 6E to provide the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-((4-thiomorpholinylcarbonyl)-leucinyl-amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 83B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 84

A. ((4-Sulphonylmorpholinyl)carbonyl)-leucine Methyl Ester.

To 2 g of the resultant compound of Example 83A in 100 ml of methylene chloride was added 2.94 g of a meta-chloroperbenzoic acid at 0 °C. After 30 min the solvent was evaporated and the ether solution was washed with 10% sodium sulfite solution and then with satd.sodium bicarbonate several times. The organic layer was dried with $MgSO_4$ and evaporation of the solvent gave the crude product which was purified by silica gel column chromatography to give the desired compound.

B. (4-Sulphonylmorpholinylcarbonyl)-leucine.

The resultant compound of Example 84A was hydrolyzed according to the procedure of Example 6E to provide the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-((4-sulphonylmorpholinylcarbonyl)-leucinyl-amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 84B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 85

A. N-Methyl-N-(2-(N,N-dimethylamino)ethyl)carbamoyl-leucine Methyl Ester.

A solution of 2.1 mmol of a-isocyanoto-leucine methyl ester (prepared according to the procedure of Example 79A) in 50 ml of dichloromethane was cooled to 0 °C and treated with 0.3 ml (2.3 mmol) of N,N,N′-trimethylethylenediamine. After being allowed to stir for 16 h, the solution was concentrated and the desired compound was isolated by flash column chromatography.

B. N-Methyl-N-(2-(N,N-dimethylamino)ethyl)carbamoyl-leucine Lithium Salt.

A solution of the resultant compound of Example 85A in dioxane was cooled to 0 °C, treated with 1.05 equiv. of aqueous lithium hydroxide (0.5 M) and stirred for 1.5 h. The resulting solution was concentrated in vacuo to give the desired compound as a white solid.

C. 2-(t-Butyloxycarbonylamino)-4-((N-methyl-N-(2-(N,N-dimethylamino)ethyl)carbamoyl)leucinyl-amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 85B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 86

A. 1-Benzyloxycarbonylamino-2,3-propanediol.

1-Amino-2,3-propanediol (15.2 g, 167 mmol) and NaOH (8.1 g, 204 mmol) in water (70 ml) at -10° C was treated dropwise with benzyl chloroformate (28.5 ml, 200 mmol) in ether (30 ml) over 20 min. The reaction was stirred at 0° C for 30 min then at room temperature for 2 h. The mixture was acidified with 2 M HCl and extracted with ethyl acetate which was washed with 0.5 M H_3PO_4 and brine, then dried over Na_2SO_4 and evaporated. Recrystallization of the residue from benzene afforded 16.59 g (44%) of the desired product as a white powder. NMR (300 MHz, CD_3OD, ppm): 3.12 (dd,1H), 3.28 (dd,1H), 3.50 (m,2H), 3.68 (m,1H), 5.08 (s,2H), 7.35 (m,5H).

B. 1-Methylamino-2,3-propanediol.

Lithium aluminum hydride (7.20 g, 189 mmol) in tetrahydrofuran (THF, 300 ml) was heated to reflux and the resultant compound from Example 86A (17.0 g, 75.5 mmol) in THF (150 ml) was added dropwise over 10 min. The mixture was refluxed for 2 h, cooled, quenched sequentially with water (10 ml), 3 M NaOH (40 ml) and water (20 ml), then filtered and concentrated. The residue was dissolved in water which was washed with ether and evaporated. Bulb to bulb distillation of the residue afforded 2.0 g (25%) of the desired compound as an oil. NMR (300 MHz, $CDCl_3$, ppm): 2.45 (s,3H), 2.68 (dd,1H), 2.77 (dd,1H), 3.61 (dd,1H), 3.72 (dd,1H), 3.78 (m,1H).

C. (N-Methyl-2,3-dihydroxypropylamino)carbonyl-leucine Methyl Ester.

Using the procedure of Example 83A but replacing thiomorpholine with the resultant compound of Example 86B gave the desired compound.

D. (N-Methyl-2,3-dihydroxypropylamino)carbonyl-leucine.

The resultant compound of Example 86C was hydrolyzed according to the procedure of Example 6E to give the desired compound.

E. 2-(t-Butyloxycarbonylamino)-4-(((N-methyl-2,3-dihydroxypropylamino)carbonyl)leucinyl-amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 86D was coupled to the resultant compound of Example 11 to give the desired compound.

Example 87

A. (N-(Benzyloxycarbonyl)pipiridin-4-yl)carbonyl-leucine Methyl Ester.

Cbz-isonipecotic acid was coupled to leucine methyl ester using the mixed anhydride procedure of Example 6F to give the desired compound.

B. (N-(Benzyloxycarbonyl)pipiridin-4-yl)carbonyl-leucine.

The resultant compound of Example 87A was hydrolyzed according to the procedure of Example 6E to give the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-(((N-(benzyloxycarbonyl)pipiridin-4-yl)carbonyl)leucinyl-amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 87B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 88

A. N-(Allyloxycarbonyl)-leucine Methyl Ester.

A solution of leucine methyl ester (5 mmol) and triethylamine (10 mmol) in dichloromethane (50 ml) was cooled to 0 °C and treated dropwise with allyl chloroformate. After addition, the solution was stirred at ambient temperature for 2 h, diluted with dichloromethane, washed successively with 1 N HCl and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated to give the desired compound.

B. N-(3-Hydroxypropyloxycarbonyl)-leucine Methyl Ester.

To a stirred 0 °C solution of the resultant compound of Example 88A (2.13 mmol) in dry tetrahydrofuran (THF, 50 ml) was added 9-borabicyclo(3.3.1)nonane (9-BBN, 25.5 ml of a 0.5 M solution in THF). The mixture was warmed to room temperature for 12 h and then cooled to 0 °C. Water (15 ml) and 3 M NaOH (4.5 ml) were added followed 2 min later by 30% H_2O_2 (5 ml). The mixture was partitioned between brine (20 ml) and ethyl acetate (100 ml). The organic phase was washed (brine), dried (Na_2SO_4), filtered, and evaporated. Silica gel chromatography provided the desired compound.

C. N-(3-Hydroxypropyloxycarbonyl)-leucine.

The resultant compound of Example 88B was hydrolyzed according to the procedure of Example 6E to give the desired compound.

D. 2-(t-Butyloxycarbonylamino)-4-(N-(3-hydroxypropyloxycarbonyl)leucinyl-amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 88C was coupled to the resultant compound of Example 11 to give the desired compound.

Example 89

A. 1,5-Di-(4-isopropylphenyl)-1,4-penten-3-one.

A solution of 3.30 g (82 mmol) of NaOH in 33 ml of water and 165 ml of 95% ethanol was treated with a mixture of 5.0 ml (33 mmol) of 4-isopropylbenzaldehyde and 1.21 ml (16.5 mmol) of acetone. The resulting solution was stirred at ambient temperature for 16 h, diluted with water, and filtered. The solid was taken up in dichloromethane, and the solution was washed with water, dried over $MgSO_4$, and concentrated to a light yellow solid. Recrystallization from hexane/ethyl acetate gave 2.15 g (41%) of the desired compound. ^1H NMR ($CDCl_3$) δ 1.27 (d, J = 7 Hz, 12 H), 2.94 (heptet, J = 7 Hz, 2 H), 7.05 (d, J = 16 Hz, 2 H), 7.28 (d, J = 10 Hz, 4 H), 7.56 (d, J = 10 Hz, 4 H), 7.72 (d, J = 16 Hz, 2 H).

B. 1,5-Di-(4-isopropylphenyl)-3-hydroxypentane.

Using the procedure of Example 3 with the resultant compound of Example 89A but replacing methyl cellusolve with methanol gave the desired compound.

Example 90

A. 1,5-Di-(4-benzyloxyphenyl)-1,4-penten-3-one.

Using the procedure of Example 89A but replacing 4-isopropylbenzaldehyde with 4-benzyloxybenzylaldehyde gave the desired compound in 70% yield after recrystallization from dichloromethane/hexane. ^1H NMR ($CDCl_3$) δ 6.95 (d, J = 16 Hz, 2 H), 7.00 (d, J = 8 Hz, 4 H), 7.3-7.5 (m, 10 H), 7.58 (d, J = 8 Hz, 4 H), 7.70 (d, J = 16 Hz, 2 H). Mass spectrum: $(M + H)^+$ = 447.

B. 1,5-Di-(4-hydroxyphenyl)-3-hydroxypentane.

Using the procedure of Example 89B with the resultant compound of Example 90A gave the desired compound (R_f 0.25, 40% ethyl acetate in chloroform) in 30% yield after silica gel chromatography using 40% ethyl acetate in chloroform. ^1H NMR ($CDCl_3$) δ 1.76 (m, 4 H), 2.55-2.7 (m, 4 H), 3.63 (m, 1 H), 4.59 (s, 2 H), 6.25 (d, J = 9 Hz, 4 H), 7.05 (d, J = 9 Hz, 4 H). Mass spectrum: $(M + NH_4)^+$ = 290.

Example 91

A. Di-(1-naphthyl)-1,4-penten-3-one.

Using the procedure of Example 89A but replacing 4-isopropylbenzaldehyde with 1-naphthaldehyde gave the desired compound in 39% yield after recrystallization from ethyl acetate/hexane. ^1H NMR ($CDCl_3$) δ 7.24 (d, J = 16 Hz, 2 H), 7.5-7.7 (m, 6 H), 7.9-8.0 (m, 6 H), 8.29 (d, J = 8 Hz, 2 H), 8.66 (d, J = 16 Hz, 2 H).

B. 1,5-Di-(1-naphthyl)-3-hydroxypentane.

Using the procedure of Example 89B with the resultant compound of Example 91A but replacing

palladium on carbon with Raney nickel gave the desired compound after silica gel chromatography.

Example 92

A. Di-(4-methoxyphenyl)-1,4-penten-3-one.

Using the procedure of Example 89A but replacing 4-isopropylbenzaldehyde with p-anisaldehyde gave the desired compound in 61% yield after recrystallization from ethyl acetate/hexane. ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 6 H), 6.92 (d, J = 9 Hz, 4 H), 6.96 (d, J = 16 Hz, 2 H), 7.58 (d, J = 9 Hz, 4 H), 7.71 (d, J = 16 Hz, 2 H).

B. 1,5-Di-(4-methoxyphenyl)-3-hydroxypentane.

Using the procedure of Example 89B with the resultant compound of Example 92A gave the desired compound after silica gel chromatography.

Example 93

A. Di-(4-bromophenyl)-1,4-penten-3-one.

Using the procedure of Example 89A but replacing 4-isopropylbenzaldehyde with 4-bromobenzaldehyde gave the desired compound in 79% yield after recrystallization from ethyl acetate/hexane. ^{1}H NMR ($CDCl_3$) δ 7.05 (d, J = 16 Hz, 2 H), 7.48 (dt, J = 9, 2 Hz, 4 H), 7.57 (dt, J = 9, 2 Hz, 4 H), 7.68 (d, J = 16 Hz, 2 H).

B. 1,5-Di-(4-bromophenyl)-3-hydroxypentane.

Using the procedure of Example 89B with the resultant compound of Example 93A but replacing palladium on carbon with 5% platinum on carbon gave the desired compound after silica gel chromatography.

Example 94

A. Cbz-alanine Ester of 3-Hydroxy-1,5-diphenylpentane.

A solution of 100 mg (0.42 mmol) of 3-hydroxy-1,5-diphenylpentane, 94 mg (0.42 mmol) of Cbz-alanine, and 10 mg (0.08 mmol) of 4-dimethylaminopyridine in 4 ml of dichloromethane was treated with 99 mg (0.51 mmol) of N-ethyl-N'-(dimethylaminoethyl) carbodiimide hydrochloride. After being stirred at ambient temperature for 7 h, the solution was diluted with ethyl acetate, washed sequentially with 10% aqueous citric acid, water, aqueous $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and concentrated to give the desired compound.

B. Alanine Ester of 3-Hydroxy-1,5-diphenylpentane

Using the procedure of Example 11 with the resultant compound of Example 94A gave the desired compound in 73% yield after silica gel chromatography using 5% methanol in chloroform. ^{1}H NMR ($CDCl_3$) δ 1.35 (d, J = 7 Hz, 3 H), 1.9-2.0 (m, 4 H), 2.6-2.7 (m, 2 H), 3.48 (q, J = 7 Hz, 1 H), 5.02 (tt, J = 7, 5 Hz, 1 H), 7.1-7.3 (m, 10 H).
Anal. Calcd. for $C_{20}H_{26}ClNO_2 \cdot 0.5H_2O$: C, 67.31; H, 7.63; N, 3.92. Found: C, 67.19; H, 7.25; N, 3.85.

Example 95

A. Boc-glycine Ester of 3-Hydroxy-1,5-diphenylpentane.

Using the procedure of Example 94A but replacing Cbz-alanine with Boc-glycine gave the desired compound.

B. Glycine Ester of 3-Hydroxy-1,5-diphenylpentane Acetate.

Using the procedure of Example 12 with the resultant compound of Example 95A gave a white solid which was taken up in dichloromethane, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Silica gel chromatography using 1.5% methanol in chloroform followed by treatment with acetic acid in chloroform gave, after concentration, the desired compouned in 79% yield. ^{1}H NMR ($CDCl_3$) δ 1.9-2.0 (m, 4 H), 2.09 (s, 3 H), 2.6-2.7 (m, 4 H), 3.32 (br s, 2 H), 3.6-3.8 (m, 2 H), 5.06 (tt, J = 7, 5 Hz, 1 H), 7.1-7.3 (m, 10 H). Mass spectrum: $(M + H)^+$ = 298.

Example 96

A. N^{α},N^{ϵ}-Di-Cbz-lysine Ester of 3-Hydroxy-1,5-diphenylpentane.

Using the procedure of Example 94A but replacing Cbz-alanine with N^{α},N^{ϵ}-Di-Cbz-lysine gave the desired compound.

B. Lysine Ester of 3-Hydroxy-1,5-diphenylpentane Diacetate.

A mixture of 180 mg (0.28 mmol) of the resultant compound of Example 96B and 50 mg of 10% palladium on carbon in 5 ml of methanol and 0.3 ml of acetic acid was stirred under an H_2 atmosphere for 16 h. The solution was filtered through Celite and concentrated to give 135 mg (98%) of the desired compound as a white solid. Mass spectrum: $(M + H)^+$ = 369.
Anal. Calcd. for $C_{27}H_{40}N_2O_6 \cdot H_2O$: C, 64.01; H, 8.36; N, 5.53. Found: C, 63.97; H, 8.13; N, 5.36.

Example 97

2-(t-Butyloxycarbonylamino)-4-((6-(Cbz-amino)hexanoyl)amino)-1,5-diphenyl-3-hydroxypentane.

N-(6-(Benzyloxycarbonylamino)hexanoic acid was coupled to the resultant compound of Example 11 using the mixed anhydride procedure of Example 54A to give the desired compound after silica gel chromatography using 75% ethyl acetate in chloroform.

Example 98

2-((3-(Benzyloxycarbonyl)-3-methylpropanoyl)amino)-4-((6-(Cbz-amino)hexanoyl)amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 97 (32 mg) was deprotected according to the procedure of Example 12 and coupled to 3-benzyloxycarbonyl-2,2-dimethylpropanoic acid (Matsushita, et. al., Heterocycles, 22, 1403 (1984) according to the mixed anhydride coupling procedure of Example 54A to give the desired compound in 28% yield after silica gel chromatography using 60% ethyl acetate in chloroform. Mass spectrum: $(M - PhCH_2O)^+ = 628$.

Example 99

2-((3-Carboxy-3-methylpropanoyl)amino)-4-(6-aminohexanoyl)amino-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 71C with the resultant compound of Example 98 gave the desired compound in 100% yield. Mass spectrum: $(M + H)^+ = 512$.

Example 100

A. (4S)-3-(4-Methylpentanoyl)-4-(2-propyl)oxazolidine-2-one.

To a stirred solution of 4-(2-propyl)-oxazolidine-2-one in anhydrous tetrahydrofuran (250 ml) under a nitrogen atmosphere at -78° C was added in a dropwise fashion a solution of n-butyllithium in hexane (50 ml, 77.4 mmol) over 5 to 10 min. After stirring an additional 20 min at -78° C, 4-methylpentanoyl chloride (85.2 mmol) was added neat. The reaction was warmed to room temperature and stirred 1 to 2 h at the temperature. The reaction was quenched by adding 100 ml of saturated aqueous ammonium chloride and the volatiles were removed by rotary evaporation. The resulting aqueous residue was extracted three times with ether and the combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. Recrystallization from hexanes/ethyl acetate provided the desired compound.

B. (4R)-3-((2-R)-2-(t-Butyloxycarbonyl)methyl-4-methylpentanoyl)-4-(2-propyl)oxazolidine-2-one.

To a stirred solution of the resultant compound of Example 100A (8.72 mmol) in anhydrous tetrahydrofuran (30 ml) under a nitrogen atmosphere at -78° C was added a solution of sodium hexamethyldisilylamide (9.6 ml, 9.59 mmol) in tetrahydrofuran. After stirring for 30 min at -78° C, t-butyl bromoacetate (2.21 g, 11.34 mmol) was added in anhydrous tetrahydrofuran and the resulting solution stirred 1 h at -78° C. The reaction was quenched by adding 20 ml of saturated aqueous ammonium chloride and

partitioned between water and ether. The aqueous layer was drawn off and extracted with ether. The combined organic phases were washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Recrystallization from acetone/hexanes provided the desired compound.

C. Benzyl-(2R)-2-(t-Butyloxycarbonyl)methyl-4-methylpentanoate.

To a stirred solution of dry benzyl alcohol (0.55 ml, 5.33 mmol) in anhydrous tetrahydrofuran (18 ml) under a nitrogen atmosphere at 0 °C was added a hexane solution of n-butyllithium (2.58 ml; 4.00 mmol). To this solution was added the resultant compound of Example 100B in anhydrous tetrahydrofuran (10 ml). After stirring 1 h at 0 °C the reaction was quenched by adding excess saturated aqueous ammonium chloride. The volatiles were removed by rotary evaporation and the resulting aqueous residue was extracted two times with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to provide an oil which was purified by chromatography on SiO_2 to give the desired compound.

D. Benzyl (2R)-2-(Carboxymethyl)-4-methylpentanoate.

The resultant compound of Example 100C (1.47 mmol) was dissolved in a 1:1 (v:v) solution (6 ml) of trifluoroacetic acid and dichloromethane and stirred at room temperature for 1 h. The volatiles were removed in vacuo to provide the desired compound. The unpurified material was of sufficient purity to employ in subsequent steps.

E. Benzyl(2R)-2-Isobutyl-3-morpholinocarbonylpropionate.

The resultant compound of Example 100D was coupled to morpholine using the mixed anhydride procedure as described in Example 6F to give the desired compound.

F. (2R)-2-Isobutyl-3-morpholinocarbonylpropionic Acid.

The resultant compound of Example 100E was hydrogenolyzed according to the procedure of Example 71C to provide the desired compound.

G. 2-(t-Butyloxycarbonylamino)-4-(N-(2-isobutyl-3-morpholinocarbonylpropionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 100F was coupled to the resultant compound of Example 11 to give the desired compound.

Example 101

A. (((4Morpholinyl)carbonyl)oxy)-4-methylpentanoic Acid Methyl Ester.

To 2-hydroxy-4-methylpentanoic acid methyl ester was added 150 ml of 12.5% phosgene in toluene

and 25 drops of dimethylformamide. After stirring for 16 h at room temperature, the solvent was evaporated and the residue chased several times with benzene. The resulting product was dissolved in methylene chloride (50 ml), cooled to 0° C and treated by dropwise addition with 3.86 g (0.044 mol) of morpholine. The reaction mixture was stirred for 2 h at 0-5° C and then distributed between 0.5 N HCl and methylene chloride. The organic phase was washed with aqueous $NaHCO_3$ and brine and evaporated to a residue. Flash chromatography on silica gel gave the desired compound.

B. (((4Morpholinyl)carbonyl)oxy)-4-methylpentanoic Acid.

The resultant compound of Example 101A was hydrolyzed according to the procedure of Example 6E to provide the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-(N-((((4-morpholinyl)carbonyl)oxy)-4-methylpentanoyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 101B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 102

A. Benzyl (2R)-2-Isobutyl-3-((N-benzyl-N-methylamino)carbonyl)propionate.

The resultant compound of Example 100D was coupled to benzylamine using the mixed anhydride procedure as described in Example 6F to give the desired compound.

B. (2R)-2-Isobutyl-3-((N-benzyl-N-methylamino)carbonyl)propionic Acid.

The resultant compound of Example 102A was hydrolyzed according to the procedure of Example 6E to provide the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-(N-(2-isobutyl-3-((N-benzyl-N-methylamino)carbonyl)propionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 102B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 103

2-Amino-4-(N-(2-isobutyl-3-((N-benzyl-N-methylamino)carbonyl)propionyl)amino)-1,5-diphenyl-3-hydroxypentane Hydrochloride.

Using the procedure of Example 12 with the resultant compound of Example 102C gave the desired

compound.

Example 104

2,4-Bis-(N-(2-isobutyl-3-((N-benzyl-N-methylamino)carbonyl)propionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 102B was coupled to the resultant compound of Example 103 to give the desired compound.

Example 105

A. Benzyl (2R)-2-Isobutyl-3-(((4-N-benzyl-N-methylamino)carbonyl)amino)propionate.

The resultant compound of Example 100D (1.47 mmol), diphenylphosphoryl azide (1.47 mmol), and triethylamine (1.47 mmol) in dry benzene (6 ml) were refluxed for 5 h to provide a solution of the derived isocyanate which was cooled to 0 °C and treated with benzylamine (1.6 mmol). The cooling bath was removed and the reaction stirred for 1 h. The reaction mixture was poured into 10% aqueous HCl and extracted two times with ether. The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated in vacuo to provide the unpurified product. The desired product was obtained in pure form after chromatography on SiO_2.

B. (2R)-2-Isobutyl-3-(((N-benzyl-N-methylamino)carbonyl)amino)propionic Acid.

The resultant compound of Example 105A was hydrolyzed according to the procedures of Example 6E to give the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-(N-(2-isobutyl-3-(((N-benzyl-N-methylamino)carbonyl)amino)propionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 105B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 106

A. Benzyl (2R)-2-Isobutyl-3-((ethoxycarbonyl)amino)propionate.

Using the procedure of Example 105A but replacing benzylamine with ethanol gave the desired compound.

B. (2R)-2-Isobutyl-3-((ethoxycarbonyl)amino)propionic Acid.

The resultant compound of Example 106A was hydrogenolyzed according to the procedure of Example 71C to give the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-(N-(2-isobutyl-3-((ethoxycarbonyl)amino)propionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 106B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 107

A. N-Benzyloxycarbonyl-N-methyl-2-aminoethanol.

To N-methylethanolamine (149 mmol) in methylene chloride (100 ml) at 0 °C was added benzyl chloroformate (70 mmol). The mixture was stirred at 0 °C for 30 min, then at room temperature for 1 h, poured into ethyl acetate, washed with 2 M HCl, saturated $NaHCO_3$ solution, and brine, then dried over Na_2SO_4 and evaporated to provide the desired compound. ^1H NMR ($CDCl_3$,TMS) δ 7.36 (m,5H), 5.14 (s,2H), 3.78 (m,2H), 3.47 (m,2H), 3.01 (s,3H).

B. 1-Methoxyethoxymethoxy-2-(N-methyl-N-benzyloxycarbonylamino)ethane.

To the resultant compound from Example 107A (66 mmol) in methylene chloride (100 ml) was added diisopropylethylamine (138 mmol) and 2-methoxyethoxymethyl chloride (132 mmol). After 4 h the mixture was evaporated, dissolved in ethyl acetate, washed with 0.5 M H_3PO_4, saturated $NaHCO_3$ solution, and brine, then dried over Na_2SO_4, and evaporated to afford the desired product as an oil, b.p. 150-170 °C (0.3 mm).

C. 1-Methylamino-2-methoxyethoxymethoxyethane.

The resultant compound from Example 107B (31 mmol) and 10% palladium on carbon (3 g) in methanol (60 ml) were stirred under a hydrogen atmosphere for 24 h. The mixture was filtered, evaporated and distilled to afford the desired product as an oil, b.p. 130-140 °C (45 mm).

D. Benzyl (2R)-2-Isobutyl-3-(N-methyl-2-methoxyethoxymethoxyethyl)aminocarbonyl)propionate.

The resultant compound of Example 100D was coupled to the resultant compound of Example 107C using the mixed anhydride procedure of Example 6F to give the desired compound.

E. (2R)-2-Isobutyl-3-(N-methyl-N-(2-methoxyethoxymethoxyethyl)aminocarbonyl)propionic Acid.

The resultant compound of Example 107D was hydrogenolyzed according to the procedure of Example 71C to give the desired compound.

F. 2-(t-Butyloxycarbonylamino)-4-(N-2-isobutyl-3-(N-methyl-N-(2-methoxyethoxymethoxyethyl)aminocarbonyl)-propipnyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 106B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 108

2-(t-Butyloxycarbonylamino)-4-(p-toluenesulfonylamino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound from Example 11 (0.05 mmol) in 2 ml of pyridine was cooled to 0 °C and treated with 0.05 mmol of p-toluenesulfonyl chloride. After 2 h, the solution was diluted with ether, washed sequentially with 1 N HCl, aqueous $NaHCO_3$, and saturated brine, dried over $MgSO_4$, and concentrated. Silica gel chromatography gave the desired compound.

Example 109

2-Amino-4-(p-toluenesulfonylanlno)-1,5-diphenyl-3-hydroxypentane Hydrochloride.

Using the procedure of Example 12 with the resultant compound of Example 108 gave the desired compound.

Example 110

2,4-Bis-(p-toluenesulfonylamino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 108 with the resultant compound of Example 109 gave the desired compound.

Example 111

2-(t-Butyloxycarbonylamino)-4-(N-((p-toluenesulfonyl)valinyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, N-(p-toluenesulfonyl)valine was coupled to the resultant compound of Example 11 to give the desired compound.

Example 112

2-Amino-4-(N-((p-toluenesulfonyl)valinyl)amino)-1,5-diphenyl-3-hydroxypentane Hydrochloride.

Using the procedure of Example 12 with the resultant compound of Example 111 gave the desired compound.

Example 113

2,4-Bis-(N-((p-toluenesulfonyl)valinyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, N-p-toluenesulfonyl)valine was coupled to the resultant compound of Example 112 to give the desired compound.

Example 114

A. N-(2-Cyanoethyl)leucine Methyl Ester.

A solution of leucine methyl ester (0.590 mmol) in acrylonitrile (2 ml) was heated at reflux. Evaporation provided a residue which was chromatographed on silica gel to give desired compound.

B. N-(3-Benzyloxycarbonylaminopropyl)leucine Methyl Ester.

The resultant compound of Example 114A (0.135 mmol) was hydrogenated (4 atmospheres H_2) over Raney Nickel (85 mg) in anhydrous methanol/ammonia (20 ml/5 ml) for 3 h. Filtration and evaporation provided the crude amine which was taken up in dichloromethane and treated with 0.14 mmol of N-(benzyloxycarbonyloxy)succinimide. After 2 h, the solution was washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Silica gel chromatography gave the desired compound.

C. N-(3-Benzyloxycarbonylaminopropyl)leucine.

The resultant compound of Example 114B was hydrolyzed according to the procedure of Example 6E to give the desired compound.

D. 2-(t-Butyloxycarbonylamino)-4-(N-(((3-benzyloxycarbonyl)aminopropyl)leucinyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 114C was coupled to the resultant compound of Example 11 to give the desired compound.

Example 115

2-(t-Butyloxycarbonylamino)-4-(N-((3-aminopropyl)leucinyl)amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 114D was hydrogenolyzed according to the procedure of Example 71C to provide the desired compound.

Example 116

A. Methyl a-Benzylacrylate.

a-Benzylacrylic acid (1.00 g, 6.17 mmol) in methanol (20 ml) was treated with $BF_3 \cdot Et_2O$ (2 ml). The mixture was heated to reflux for 14 h, cooled, and poured into saturated $NaHCO_3$ solution. Extraction with ether followed by drying over Na_2SO_4 and evaporation afforded 1.03 g (95%) of a mobile oil. ^{1}NMR ($CDCl_3$) δ 7.17-7.35 (m,5H), 6.23 (m,1H), 5.47 (m,1H), 3.74 (s,3H), 3.63 (s,2H).

B. Methyl 2-Benzyl-3-(N-methoxyl-N-methylamino)propionate.

The resultant compound from Example 116A (800 mg, 4.54 mmol), N-methyl,O-methylhydroxylamine hydrochloride (0.57 g, 5.4 mmol), and $NaHCO_3$ (0.46 g, 5.48 mmol) in dimethylsulfoxide (5 ml) were heated at 130° C for 20 h. The mixture was diluted with ethyl acetate, washed with water, saturated $NaHCO_3$ solution and brine, and then was dried over Na_2SO_3 and evaporated. Chromatography of the residue on silica gel with 10% ethyl acetate in hexane afforded 226 mg (21%) of a mobile oil. ^{1}H NMR ($CDCl_3$) δ 7.10-7.30 (m,5H), 3.60 (s,3H), 3.47 (s,3H), 2.80-3.10 (m,4H), 2.60 (dd,1H), 2.55 (s,3H).

C. 2-Benzyl-3-(N-methoxyl-N-methylamino)propionic Acid.

Using the procedure of Example 117B with the resultant compound from Example 116B gave the desired product. ^{1}H NMR ($CDCl_3$) δ 7.10-7.35 (m,5H), 3.58 (s,3H), 2.62 (s,3H).

D. 2-(t-Butyloxycarbonylamino)-4-(N-(2-benzyl-3-(N-methoxyl-N-methylamino)propionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 116C was coupled to the resultant compound of Example 11 to give the desired compound.

Example 117

A. Methyl 2-Benzyl-3-pyrazol-1-ylpropionate.

Using the procedure of Example 116B but replacing N-methyl,O-methylhydroxylamine hydrochloride and $NaHCO_3$ with pyrazole provided the desired product as an oil. ^{1}H NMR ($CDCl_3$) δ 7.52 (d,1H), 7.10-7.35 (m,6H), 6.10 (dd,1H), 4.38 (dd,1H), 4.24 (dd,1H), 3.57 (s,3H), 3.37 (m,1H), 2.98 (dd,1H), 2.82 (dd,1H).

B. 2-Benzyl-3-pyrazol-1-ylpropionic Acid.

The resultant compound from Example 117A (100.0 mg, 0.409 mmol) in dioxane (2 ml) at 0 °C was treated with $LiOH \cdot H_2O$ (22.0 mg, 0.524 mmol) in water (1 ml). After 1 h at 0 °C and 30 min at room temperature the solvent was evaporated and the residue was taken up in water, the pH was adjusted to pH 3-4, and the mixture was extracted with $CHCl_3$ which was dried over Na_2SO_4 and evaporated to afford 96 mg (100%) of a solid. ^1H NMR ($CDCl_3$) δ 7.56 (d,1H), 7.10-7.35 (m,6H), 6.26 (dd,1H), 4.30 (m,2H), 3.34 (m,1H), 3.12 (dd,1H), 2.72 (dd,1H).

C. 2-(t-Butyloxycarbonylamino)-4-(N-(2-benzyl-3-pyrazol-1-ylpropionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 117B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 118

A. Methyl 2-Benzyl-3-tert-butylmercaptopropionate.

To sodium (3.05 g, 133 mmol) in methanol (135 ml) was added tert-butylmercaptan (17.0 ml, 151 mmol). After 20 min methyl a-benzylacrylate (17.05 g, 96.8 mmol) in methanol (100 ml) was added and after 1 h at room temperature the mixture was heated at reflux for 17 h. After cooling, the mixture was acidified with 2 M HCl (70 ml), concentrated, taken up in ether, washed with water and brine, then dried over $MgSO_4$ and evaporated to 23.59 g (92%) of an oil. ^1H NMR ($CDCl_3$) δ 7.15-7.35 (m,5H), 3.63 (s,3H), 2.60-3.05 (m,5H), 1.28 (s,9H).

B. Methyl 2-Benzyl-3-tert-butylsulfonylpropionate.

To the resultant compound from Example 118A (270 mg, 1.01 mmol) in methanol (6 ml) and water (5 ml) at 0 °C was added potassium peroxymonosulfate (1.845 g, 6 mmol) in portions. After 15 min at 0 °C and 24 h at room temperature the mixture was filtered, diluted with water, and extracted with CH_2Cl_2 which was washed with brine, dried over $MgSO_4$, and evaporated to 300 mg (99%) of an oil. ^1H NMR δ 7.15-7.35 (m,5H), 3.68 (s,3H), 3.45 (m,2H), 3.12 (dd,1H), 2.98 (m,2H), 1.37 (s,9H).

C. 2-Benzyl-3-tert-butylsulfonylpropionic Acid.

The resultant compound from Example 118B (282 mg, 0.95 mmol) in 6 M HCl (2 ml) and acetic acid (0.4 ml) was heated at reflux for 16 h. The mixture was cooled and filtered and the resulting solid was recrystallized from methycyclohexane/ethyl acetate to afford 152 mg (56%) of the desired product, m.p. 147-148 °C.

D. 2-(t-Butyloxycarbonylamino)-4-(N-(2-benzyl-3-tert-butylsulfonylpropionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 118C was coupled to the resultant compound of Example 11 to give the desired compound.

Example 119

2-(t-Butyloxycarbonylamino)-4-(N-(3-phenyl-2-(phenylmethyl)propionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, dibenzylacetic acid was coupled to the resultant compound of Example 11 to give the desired compound.

Example 120

1,5-Di-(4-isopropylphenyl)-3-(methoxymethyl)pentane.

Using the procedure of Example 51 but replacing 1,5-diphenyl-3-pentanol with the resultant compound of Example 89B gave the desired compound.

Example 121

1,5-Di-(1-naphthyl)-3-(methoxymethyl)pentane.

Using the procedure of Example 51 but replacing 1,5-diphenyl-3-pentanol with the resultant compound of Example 91B gave the desired compound.

Example 122

1,5-Di-(4-methoxyphenyl)-3-(methoxymethyl)pentane.

Using the procedure of Example 51 but replacing 1,5-diphenyl-3-pentanol with the resultant compound of Example 92B gave the desired compound.

Example 123

1,5-Di-(4-bromophenyl)-3-(methoxymethyl)pentane.

Using the procedure of Example 51 but replacing 1,5-diphenyl-3-pentanol with the resultant compound of Example 93B gave the desired compound.

Example 124

1,5-Diphenyl-3-(thiomethoxymethyl)pentane.

1,5-Diphenyl-3-hydroxypropentane was treated with sodium hydride followed by chloromethyl methyl sulfide and sodium iodide according to the procedure of Corey and Bock (*Tetrahedron Lett.* **1975**, 3269) to provide the desired compound.

Example 125

1,5-Diphenyl-3-(2-methoxyethoxymethyl)pentane.

Using the procedure of Example 51 but replacing chloromethyl methyl ether with 2-methoxyethoxymethyl chloride gave the desired compound.

Example 126

A. Methyl 2-Fluoro-3-phenylpropanoate.

Using the procedure of Example 34B but replacing the resultant compound of Example 34A with methyl 3-phenyllactate provided the desired compound.

B. 2,3-Epoxy-4-fluoro-1,5-diphenylpentane.

The resultant compound of Example 126B treated with α-lithio-2-phenylethyl phenyl sulfoxide according to the procedure of Bravo et. al. (*J. Chem. Soc.*, Perkin Trans. I, **1989**, 1201) to provide the desired compound.

C. 2-Azido-1,5-diphenyl-4-fluoro-3-hydroxypentane.

Using the procedure of Example 10C with the resultant compound of Example 126B gave the desired compound.

Example 127

2-Amino-1,5-diphenyl-4-fluoro-3-hydroxypentane.

Using the procedure of Example 10D with the resultant compound of Example 126C gave the desired compound.

Example 128

2-(N-Cbz-valinyl)amino-1,5-diphenyl-4-fluoro-3-hydroxypentane.

Using the procedure of Example 55 but replacing the resultant compound of Example 11 with the resultant compound of Example 127 gave the desired compound.

Example 129

2-(N-Cbz-valinyl)amino-1,5-diphenyl-4-fluoro-3-pentanone.

According to the procedure of Thaisrivongs et. al. (*J. Med. Chem.* 1986, *29*, 2080), the resultant compound of Example 128 was oxidized with oxalyl chloride/dimethyl sulfoxide to provide the desired compound.

Example 130

A. Benzyl α-Isopropylacrylate.

α-Isopropylacrylic acid (13 mmol) in dry ether (40 ml) was treated with dicyclohexylcarbodiimide (12 mmol), benzyl alcohol (12 mmol) and 4-dimethylaminopyridine (2.5 mmol). After stirring at ambient temperature for 44 h, the mixture was filtered and evaporated. Silica gel chromatography provided the desired compound.

B. Benzyl 3-Acetylmercapto-2-isopropylpropionate.

The resultant compound of Example 130A (27 mmol) in dry ether (10 ml) was treated with thiolacetic acid (42 mmol) and pyridine (28 mmol). After 5 days, the mixture was concentrated in vacuo and chromatographed on silica gel to provide the desired compound.

C. 2-Benzyloxycarbonyl-3-methylbut-1-ylsulfonyl Chloride.

Chlorine was bubbled into a mixture of the resultant compound of Example 130B (25 mmol) in water (250 ml) for 30 min at ambient temperature followed by nitrogen which was bubbled through the mixture for 15 min. The mixture was extracted with methylene chloride which was dried over $MgSO_4$ and concentrated to provide the desired compound which was used without further purification.

D. Benzyl 2-Isopropyl-3-(4-methylpiperizin-1-ylsulfonyl)propionate.

A solution of the resultant compound of Example 130C (2.8 mmol) in 10 ml of dichloromethane was cooled to -10 °C and treated with 1-methylpiperazine (8.5 mmol). After 30 min, the solution was concentrated in vacuo, taken up in ethyl acetate, washed sequentially with aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO4, and concentrated. Silica gel chromatography provided the desired compound.

E. 2-Isopropyl-3-(4-methylpiperizin-1-ylsulfonyl)propionic Acid.

The resultant compound of Example 130D was hydrogenolyzed according to the procedure of Example 71C to provide the desired compound.

F. 2-(t-Butyloxycarbonylamino)-4-(N-((2-isopropyl-3-(4-methylpiperizin-1-yl)sulfonyl)propionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 130E was coupled to the resultant compound of Example 11 to give the desired compound.

Example 131

A. Benzyl 2-Isopropyl-3-(morpholin-4-ylsulfonyl)propionate.

Using the procedure of Example 130D but replacing 1-methylpiperazine with morpholine gave the desired compound.

B. 2-Isopropyl-3-(morpholin-4-ylsulfonyl)propionic Acid.

The resultant compound of Example 131A was hydrogenolyzed according to the procedure of Example 71C to provide the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-(N-((2-isopropyl-3-(morpholin-4-yl)sulfonyl)propionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 131B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 132

A. Benzyl 2-Isopropyl-3-((benzylamino)sulfonyl)propionate.

Using the procedure of Example 130D but replacing 1-methylpiperazine with benzylamine gave the desired compound.

B. 2-Isopropyl-3-((benzylamino)sulfonyl)propionic Acid.

The resultant compound of Example 132A was hydrolyzed according to the procedure of Example 6E to provide the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-(N-((2-isopropyl-3-(benzylamino)sulfonyl)propionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 132B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 133

2-Amino-4-(N-((2-isopropyl-3-(4-methylpiperizin-1-yl)sulfonyl)propionyl)amino)-1,5-diphenyl-3-hydroxypentane Dihydrochloride.

Using the procedure of Example 12 with the resultant compound of Example 130F provided the desired compound.

Example 134

2,4-Bis-(N-((2-isopropyl-3-(4-methylpiperizin-1-yl)sulfonyl)propionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 130E was coupled to the resultant compound of Example 133 to give the desired compound.

Example 135

2-Amino-4-(N-((2-isopropyl-3-(benzylamino)sulfonyl)propionyl)amino)-1,5-diphenyl-3-hydroxypentane Dihydrochloride.

Using the procedure of Example 12 with the resultant compound of Example 132C provided the desired compound.

Example 136

2,4-Bis-(N-((2-isopropyl-3-(benzylamino)sulfonyl)propionyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 132B was coupled to the resultant compound of Example 135 to give the desired compound.

Example 137

A. N-((4-Methylpiperazin-1-yl)sulfamoyl)valine Benzyl Ester.

A solution of valine benzyl ester p-toluenesulfonate (5 mmol) in dichloromethane (50 ml) was cooled to 0° C and treated sequentially with diisopropylethylamine (12 mmol) and 4-methylpiperazinesulfamoyl chloride. After being stirred for 16 h at ambient temperature, the solution was diluted with ethyl acetate, washed sequentially with 1N HCl, water, and aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Silica gel chromatography provided the desired compound.

B. N-((4-Methylpiperazin-1-yl)sulfamoyl)valine.

The resultant compound of Example 137A was hydrogenolyzed according to the procedure of Example 71C to provide the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-(N-(((4-methylpiperazin-1-yl)sulfamoyl)valinyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 137B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 138

2-Amino-4-(N-(((4-methylpiperazin-1-yl)sulfamoyl)valinyl)amino)-1,5-diphenyl-3-hydroxypentane Dihydrochloride.

Using the procedure of Example 12 with the resultant compound of Example 137C provided the desired compound.

Example 139

2,4-Bis-(N-(((4-methylpiperazin-1-yl)sulfamoyl)valinyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 137B was coupled to the resultant compound of Example 138 to give the desired compound.

Example 140

2,4-Bis-N-(valinyl)amino-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 70 was hydrogenolyzed according to the procedure of Example 71C to provide the desired compound (R_f 0.1, 10% methanol in chloroform) as a white solid, m.p. 131-132° C.

Example 141

2-Amino-5-(t-butyloxycarbonylamino)-3,4-dihydroxy-1,6-diphenyl-3-hexane.

A mixture of 0.13 g of the resultant compound of Example 17B and 0.13 g of 10% palladium on carbon in 50 ml of ethyl acetate was shaken under 4 atmospheres of H_2 for 4 h. The resulting mixture was filtered through Celite and concentrated in vacuo to provide 72 mg (86%) of the desired compound as a 1:1 mixture of diastereomers. Mass spectrum: $(M + H)^+ = 401$.

Example 142

A. N-(3-pPhenylpropionyl)valine Benzyl Ester.

Using the procedure of Example 137A but replacing 4-methylpiperazinesulfamoyl chloride with dihydrocinnamoyl chloride gave the desired compound.

B. N-(3-Phenylpropionyl)valine.

The resultant compound of Example 142A was hydrogenolyzed according to the procedure of Example 71C to provide the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-(N-((3-phenylpropionyl)valinyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 142B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 143

N,N-Di-(2-phenylethyl)-O-(methoxymethyl)hydroxylamine.

Using the procedure of Example 51 but replacing 1,5-diphenyl-3-pentanol with the resultant compound of Example 30B gave the desired compound.

Example 144

A. N-((Benzylamino)carbonyl)valine Methyl Ester.

Using the procedure of Example 83A but replacing leucine methyl ester hydrochloride with valine methyl ester hydrochloride and replacing thiomorpholine with benzylamine provided the desired compound.

B. N-((Benzylamino)carbonyl)valine.

The resultant compound of Example 144A was hydrolyzed according to the procedure of Example 6E to provide the desired compound.

C. 2-(t-(Butyloxycarbonylamino)-4-(N-(((benzylamino)carbonyl)valinyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 144B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 145

A. N-(3-Phenylpropyl)valine Benzyl Ester.

A mixture of dihydrocinnamaldehyde (7 mmol), valine benzyl ester dihydrochloride (7 mmol), anhydrous sodium acetate (0.7 g, 21 mmol), and sodium cyanoborohydride (11 mmol) in 200 mL of isopropyl alcohol was stirred at ambient temperature. After 16 h, an additional 0.2 g portion of sodium cyanoborohydride was added and stirring was continued for 4.5 h. After removal of the solvent in vacuo, the residue was taken up in ethyl acetate, washed sequentially with saturated aqueous $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and concentrated. Silica gel chromatography gave the desired compound.

B. N-(3-Phenylpropyl)valine.

The resultant compound of Example 145A was hydrogenolyzed according to the procedure of Example 71C to provide the desired compound.

C. 2-(t-Butyloxycarbonylamino)-4-(N-((3-phenylpropyl)valinyl)amino)-1,5-diphenyl-3-hydroxypentane.

According to the carbodiimide coupling procedure of Example 55, the resultant compound of Example 145B was coupled to the resultant compound of Example 11 to give the desired compound.

Example 146

2,4-Bis-(Cbz-valinyl-amino)-1,5-diphenyl-3-((methoxy)methoxy)pentane.

A solution of 22 mg of the resultant compound of Example 70 in 1 ml of dichloromethane was treated with 0.07 ml of ethyldiisopropylamine and 0.03 ml of chloromethyl methyl ether. The resulting solution was heated at reflux for 1 h. The cooled solution was concentrated in vacuo to give 26 mg of a crude solid which was recrystallized from ethyl acetate/chloroform to provide 15 mg of the desired compound (R_f 0.6, 10% methanol in chloroform) as a white solid, m.p. 197-198° C. Mass spectrum: $(M + H)^+ = 781$.
Anal. Calcd for $C_{45}H_{56}N_4O_8 \cdot 1.5H_2O$: C, 66.89; H, 7.36; N, 6.93. Found: 66.96; H, 6.76; N, 6.77.

Example 147

2,2-Di-(2-phenylethyl)-1,3-dioxolane.

A solution of 135 mg (0.6 mmol) of 1,5-diphenyl-3-pentanone, 0.2 ml of ethylene glycol, and 10 mg of p-toluene sulfonic acid monohydrate was refluxed with azeotropic removal of water. After separation of water was completed, the solution was diluted with ethyl acetate, washed sequentially with aqueous NaHCO and water, dried over Na_2SO_4, and concentrated to provide the desired compound. ^1H NMR ($CDCl_3$) δ 2.0 (m, 4 H), 2.71 (m, 4 H), 4.03 (s, 4 H), 7.15-7.3 (m, 10 H). Mass spectrum: $(M + H)^+$ = 283.

Example 148

2-(Acetylamino)-4-(t-butyloxycarbonylamino)-1,5-diphenyl-3-hydroxypentane.

A solution of 20 mg of the resultant compound of Example 11 and 0.05 ml of triethylamine in 1 ml of dichloromethane was cooled to 0 °C and treated with 0.01 ml of acetic anhydride. After 30 min, the solution was partitioned between water and dichloromethane, and the organic phase was dried over Na_2SO_4 and concentrated to give 23 mg (100%) of the desired compound (R_f 0.5, 10% methanol in chloroform). Mass spectrum: $(M + H)^+$ = 413.

Example 149

A. 3-(tert-Butyldimethylsilyloxy)-1,6-diphenyl-4-hydroxyhexane.

A solution of 2-phenylethylmagnesium bromide (prepared from 0.4 ml of 2-(bromoethyl)benzene and 90 mg of magnesium) in tetrahydrofuran was cooled to 0 °C and treated with a solution of 0.35 g of the resultant compound of Example 6C in tetrahydrofuran. After being stirred at ambient temperature for 1 h, the solution was heated at reflux for 4 h, treated with saturated aqueous ammonium chloride, extracted with ether, washed with saturated brine, dried over $MgSO_4$, and concentrated. Silica gel chromatography using ethyl acetate/hexane gave the desired compound.

B. 3,4-Dihydroxy-1,6-diphenylhexane.

A solution of the resultant compound of Example 149A (30 mg, 0.078 mmol) was deprotected according to the procedure of Example 6G to provide the desired compound as a 3:1 mixture of diastereomers. Recrystallization from chloroform/ethyl acetate provided the desired compound as a single isomer, m.p. 128.5-129 °C. ^1H NMR ($CDCl_3$) δ 1.76 (m, 4 H), 1.82 (d, J = 5 Hz, 2 H), 2.63 (dt, J = 14, 8 Hz, 2 H), 2.85 (ddd, J = 14, 9, 6 Hz, 2 H), 3.62 (m, 2 H), 7.15-7.3 (m, 10 H). Mass spectrum: $(M + NH_4)^+$ = 288.

Example 150

4,5-Di-(2-phenylethyl)-1,3-dioxolane.

The resultant compound of Example 149 was treated with paraformaldehyde and H_2SO_4 in acetic acid according to the procedure of Hough, et. al. (*J. Chem. Soc.*, **1952**, 1525) to provide the desired compound.

Example 151

4,4-Di-(2-phenylethyl)-1,3-dioxolane.

The resultant compound of Example 20 was treated with paraformaldehyde and H_2SO_4 in acetic acid according to the procedure of Hough, et. al. (*J. Chem. Soc.*, **1952**, 1525) to provide the desired compound.

Example 152

3,3-Dimethoxy-1,5-diphenylpentane.

1,5-Diphenyl-3-pentanone was treated with HCl in anhydrous methanol according to procedure of Cameron et. al. (*J. Chem. Soc.* 1953, 3864) to provide the desired compound.

Example 153

2-(t-Butyloxycarbonylamino)-4-(((β,β-di-Me)-β-Ala)leucinyl-amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 78D was hydrogenolyzed according to the procedure of Example 71C to provide the desired compound.

Example 154

2,4-Bis-(Cbz-leucinyl-asparaginyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procdure of Example 12 with the resultant compound of Example 65 gave a crude amine hydrochloride which was coupled to Cbz-Leu-Asn-OH according to the procedure of Example 55 to give, after silica gel chromatography using methanol/ chloroform, the desired compound (R_f 0.7, 10% methanol in chloroform) as a white solid, m.p. 250-251. Mass spectrum $(M+H)^+$ = 993.

Example 155

A. Bis-{(2-t-butyloxycarbonylamino)-3-phenylpropyl}sulfide.

A solution of 2.30 g (7.0 mmol) of 2-(t-butyloxycarbonylamino)-3-phenylpropyl methanesulfonate (*Tetrahedron Lett.* **1986**, *27*, 2095) and 0.84 g (3.5 mmol) of sodium sulfide nonahydrate in 75 ml of 2:1 tetrahydrofuran/methanol was heated at reflux for 2.5 h. The cooled solution was concentrated in vacuo, partitioned between ethyl acetate and water, washed with saturated brine, dried over $MgSO_4$, and concentrated. Silica gel chromatography using 20% ethyl acetate in hexane provided 0.42 g (24%) of the desired compound. Mass spectrum: $(M+H)^+ = 501$.

B. Bis-((2-t-butyloxycarbonylamino)-3-phenylpropyl)sulfone.

A solution of the resultant compound of Example 155A (404 mg, 0.81 mmol) in 10 ml of dichloromethane was treated with 0.40 g of 80% m-chloroperbenzoic acid. After being stirred for 16 h at ambient temperature, the solution was diluted with dichloromethane, washed sequentially with 10% $Na_2S_2O_3$/3N NaOH and water, dried over $MgSO_4$, and concentrated to give 0.36 g (84%) of the desired compound (R_f 0.25, 15% ethyl acetate in chloroform) as a white solid, m.p. 227-228 °C (dec). Mass spectrum: $(M+H)^+ = 533$.
Anal. Calcd. for $C_{28}H_{40}N_2O_6S \cdot 0.75H_2O$: C, 61.57; H, 7.66; N, 5.13. Found: C, 61.65; H, 7.33; N, 4.93.

Example 156

A. Bis-((2-benzyloxycarbonyl)-3-phenylpropyl)sulfide.

Using the procedure of Example 155A but replacing 2-(t-butyloxycarbonylamino)-3-phenylpropyl methanesulfonate with benzyl α-benzylacrylate provided the desired compound after silica gel chromatography.

B. Bis-((2-benzyloxycarbonyl)-3-phenylpropyl)sulfone.

Using the procedure of Example 155B with the resultant compound of Example 156A gave the desired compound.

Example 157

Bis-((2-t-butyloxycarbonylamino)-3-phenylpropyl)sulfoxide.

Using the procedure of Example 2 with the resultant compound of Example 155A provided the desired compound.

Example 158

Bis-((2-benzyloxycarbonyl)-3-phenylpropyl)sulfoxide.

Using the procedure of Example 2 with the resultant compound of Example 156A provided the desired

compound.

Example 159

A. N,N-Bis-((2-methoxycarbonyl)-3-phenylpropyl)-O-benzylhydroxylamine.

The resultant compound from Example 116A (4 mmol), O-benzylhydroxylamine hydrochloride (2 mmol), and $NaHCO_3$ (2.2 mmol) in dimethylsulfoxide (5 ml) were heated at 130° C for 20 h. The mixture was diluted with ethyl acetate, washed with water, saturated $NaHCO_3$ solution and brine, and then was dried over Na_2SO_3 and evaporated. Silica gel chromatography provided the desired compound.

B. N,N-Bis-((2-methoxycarbonyl)-3-phenylpropyl)hydroxylamine.

The resultant compound of Example 159A (1 mmol) was treated with 10 ml of 30% HBr in acetic acid and stirred at ambient temperature for 4 h. After removal of the solvent in vacuo, the residue was partitioned between ethyl acetate and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Silica gel chromatography provided the desired compound.

Example 160

A. α-Isocyanato-valine Methyl Ester.

A suspension of L-valine methyl ester hydrochloride (10 g) in toluene (400 ml) was heated to 100° C and phosgene gas was bubbled into the reaction mixture. After approximately 6 h, the mixture became homogeneous. The bubbling of phosgene was continued for 10 more min, then the solution was cooled with the bubbling of N_2 gas. The solvent was then evaporated and the residue chased with toluene two times. Evaporation of solvent gave 14.2 g of the crude desired compound.

B. N-((4-Pyridinyl)methoxycarbonyl)-valine Methyl Ester.

A solution of 0.73 g (4.65 mmol) of the resultant compound of Example 160A and 0.51 g (4.65 mmol) of pyridine-4-methanol in 30 mL of toluene was heated at reflux under N_2 atmosphere for 4 h. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography using 2% methanol in chloroform to give 1.01 g (82%) of the desired compound as an oil. ^1H NMR ($CDCl_3$) δ 0.91 (d, J = 7 Hz, 3 H), 0.99 (d, J = 7 Hz, 3 H), 2.19 (m, 1 H), 3.76 (s, 3 H), 4.31 (dd, J = 9, 5 Hz, 1 H), 5.12 (s, 2 H), 5.37 (br d, 1 H), 7.25 (d, J = 6 Hz, 2 H), 8.60 (d, J = 6 Hz, 2 H).

C. N-((4-Pyridinyl)methoxycarbonyl)-valine Lithium Salt.

A solution of 50.8 mg (0.191 mmol) of the resultant compound of Example 160B in 0.75 ml of dioxane was treated with 0.46 ml (0.23 mmol) of 0.5 M aqueous lithium hydroxide. The resulting solution was stirred overnight at ambient temperature and concentrated in vacuo to provide the desired compound.

D. 2-(N-((4-Pyridinyl)methoxycarbonyl)-valinyl-amino)-4-(Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

A solution of the resultant compound of Example 160C (0.191 mmol), 94 mg (0.97 mmol) of the resultant compound of Example 69, and 31 mg (0.23 mmol) of 1-hydroxybenzotriazole in 2 ml of dimethylformamide was treated under N_2 atmosphere with 44 mg (0.23 mmol) of N-ethyl-N'-(dimethylaminopropyl) carbodiimide hydrochloride and stirred overnight at ambient temperature. The resulting solution was taken up in ethyl acetate, washed sequentially with aqueous $NaHCO_3$, H_2O, and saturated brine, dried over Na_2SO_4, and concentrated in vacuo. Chromatography on silica gel using 3% methanol in chloroform provided 119 mg (87%) of the desired compound (R_f 0.19, 5% methanol in chloroform) as a white solid, m.p. 170-172° C (dec). Mass spectrum: $(M + 1)^+ = 738$.
Anal. Calcd for $C_{42}H_{51}N_5O_7 \cdot 0.5H_2O$: C, 67.54; H, 7.02; N, 9.38. Found: C, 67.53; H, 7.00; N, 9.39.

Example 161

A. N-((3-Pyridinyl)methoxycarbonyl)-valine Methyl Ester.

Using the procedure of Example 160B but replacing pyridine-4-methanol with pyridine-3-methanol provided the desired compound as an oil after silica gel chromatography using 2% methanol in chloroform. ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 7 Hz, 3 H), 0.98 (d, J = 7 Hz, 3 H), 2.16 (m, 1 H), 3.65 (s, 3 H), 4.30 (dd, J = 9, 5 Hz, 1 H), 5.14 (s, 2 H), 5.30 (br d, 1 H), 7.30 (dd, J = 8, 5 Hz, 1 H), 7.70 (br d, J = 8 Hz, 1 H), 8.58 (dd, J = 4, 1 Hz, 1 H), 8.63 (br s, 1 H).

B. N-((3-Pyridinyl)methoxycarbonyl)-valine Lithium Salt.

Using the procedure of Example 160C with the resultant compound of Example 161A provided the desired compound.

C. 2-(N-((3-Pyridinyl)methoxycarbonyl)-valinyl-amino)-4-(Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 160D but replacing the resultant compound of Example 160C with the resultant compound of Example 161B provided, after silica gel chromatography using 3% methanol in chloroform, 113 mg (94%) of the desired compound (R_f 0.21, 5% methanol in chloroform) as a white solid, m.p. 177-178° C. Mass spectrum: $(M + 1)^+ = 738$.
Anal. Calcd for $C_{42}H_{51}N_5O_7 \cdot 0.5H_2O$: C, 67.54; H, 7.02; N, 9.38. Found: C, 67.35; H, 6.90; N, 9.35.

Example 162

A N-((2-Pyridinyl)methoxycarbonyl)-valine Methyl Ester.

Using the procedure of Example 160B but replacing pyridine-4-methanol with pyridine-2-methanol provided 0.72 g (54%) of the desired compound as an oil after silica gel chromatography using 2% methanol in chloroform. ^1H NMR ($CDCl_3$) δ 0.91 (d, J = 7 Hz, 3 H), 0.98 (d, J = 7 Hz, 3 H), 2.19 (m, 1 H), 3.75 (s, 3 H), 4.32 (dd, J = 9, 5 Hz, 1 H), 5.24 (s, 2 H), 5.39 (br d, 1 H), 7.23 (ddd, J = 8, 4, 1 Hz, 1 H), 7.37 (d, J = 8 Hz, 1 H), 7.70 (td, J = 8, 2 Hz, 1 H), 8.60 (br d, 1 H).